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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/568,745	IDENO ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-24* is/are pending in the application.

4a) Of the above claim(s) *14,17-19 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,13,15,16,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-15-10 and 6-7-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed March 1, 2010 are acknowledged.

   Claims 1-10 and 12-24 are pending.

   Claims 1-10, 12, 13, 15, 16, 20 and 21 are under examination wherein the elected species of fibronectin fragment is SEQ ID NO: 13 and wherein the method includes a step of diluting a cell culture solution.

   Claims 14, 17-19 and 22-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected Group or species of invention.

2. The previous grounds of rejection can be found in the Office Action mailed November 27, 2009.

   The previous rejections under 35 U.S.C. § 112, 2nd paragraph and 35 U.S.C. § 102(b) have been withdrawn in view of applicant's amendments to the claims.

   The previous obviousness type double patenting rejections have also been withdrawn in view of applicant's amendments to the claims.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 12, 13, 15, 16, 20 and 21 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of fibronectin "fragments", or polypeptides having a "substitution, deletion, insertion, or addition to one or more amino acids" of a fibronectin fragment which "comprise a cell adhesion activity and/.or a heparin binding activity," essentially for the reasons of record as put forth in the Office Action mailed November 27, 2009.

   Applicant argues based on the teachings of the instant application and the knowledge in the art an ordinary artisan "is well aware…which amino acid domains are responsible for the activity of fibronectin fragments having cell adhesion activity and/or a heparin binding activity." (see remarks page 9, 3rd paragraph).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed November 27, 2009.

Applicant's argument is not found convincing because the examiner maintains that the skilled artisan is ***not*** "well aware…which amino acid domains are responsible for the activity of fibronectin fragments having cell adhesion activity and/or a heparin binding activity" when considering the large genus of all fibronectin fragments encompassed in the breadth of the claimed method which including, e.g., fibronectin fragments derived from the type I and II homology repeats of fibronectin as well as type III fibronectin fragments having a "substitution, deletion, insertion, or addition to one or more amino acids". Applicant has not put forth an argument based on objective evidence about what structure of fibronectin the skilled artisan would be "well aware" is sufficient for "cell adhesion activity and/or a heparin binding activity." In this regard it is noted that "arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984)."

In contrast, the previous rejection of record described how the skilled artisan cannot visualize the members of the genus of "fibronectin fragments" as claimed previously; likewise the skilled artisan cannot visualize the members of the genus of "fibronectin fragments comprising a cell adhesion activity and/or a heparin binding activity" encompassed by the instant claims essentially for the reasons of record.

If claims merely recite a "description of the problem to be solved while claiming all solutions to it" and "cover any compound later actually invented and determined to fall within the claim's functional boundaries," they have not met the description requirement. see *Ariad Pharms. Co. v. Eli Lilly & Co.*, 94 U.S.P.Q.2d 1161, 1172 (Fed. Cir. 2010) (en banc), at 1172.

Similarly, see *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function … does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is"). Also, possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004).

Moreover, according to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, MPEP 2163 II.A.3a.ii.

5. Claims 1-10, 12, 13, 15, 16, 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for preparing a cytotoxic lymphocyte characterized in that the method comprises a step of induction from peripheral blood mononuclear cells or naïve T cells which can be formed into the cytotoxic lymphocytes comprising culturing the peripheral blood mononuclear cells or naïve T cells which have an ability of differentiating into the cytotoxic lymphocytes with a medium containing serum and plasma at a total concentration of 0% by volume or more and less than 5% by volume, in the presence of fibronectin or SEQ ID NO: 13,

does not reasonably provide enablement for

a method for preparing a cytotoxic lymphocyte characterized in that the method comprises a step of induction from any precursor cells which can be formed into the cytotoxic lymphocytes comprising culturing the precursor cells which have an ability of differentiating into the cytotoxic lymphocytes with a medium containing serum and plasma at a total concentration of 0% by volume or more and less than 5% by volume, in the presence of any fibronectin fragment comprising a cell adhesion activity and/or a heparin binding activity.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or

direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The instant claims are drawn a method for preparing a cytotoxic lymphocyte characterized in that the method comprises the step of carrying out at least one step selected from the group consisting of induction from a precursor cell which can be formed into the cytotoxic lymphocyte…comprising culturing the precursor cells which have an ability of differentiating into the lymphocyte with a medium containing serum and plasma at a total concentration of 0% by volume or more and less than 5% by volume, in the presence of fibronectin, a fragment thereof or a mixture thereof, wherein said fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity.

As to practicing the claimed invention with any fibronectin fragment, applicant argues "…the claims are amended to specify that the fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity. Accordingly, the claims only encompass fibronectin fragments having functions that the Examiner recognizes could be predictably used in the claimed method."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed November 27, 2009.

Applicant argument is not found convincing because the previous Office Action did not recognize any fibronectin fragment comprises a cell adhesion activity and/or a heparin binding activity could be used in the claimed method.

Rather, what was said in the previous Office Action in the paragraph bridging pages 4-5 was that "the specification only provides examples utilizing type III fibronectin fragments from the cell binding or heparin binding domain of the polypeptide. Furthermore, the only disclosure of a fragment is a single methionine addition linking various type III fibronectin fragments. This is not commensurate in scope with the instant claims which encompass preparing cytotoxic lymphocytes with any fibronectin fragment, or any substation, addition, or deletion to said fragments. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation."

The instant claims are still not enabled because the skilled artisan cannot make the vast genus of "fibronectin fragments comprising a cell adhesion activity and/or a heparin binding activity" without resorting to undue experimentation. For example, as shown in Figure 1 of

the instant specification the N-terminal Type I repeat of fibronectin comprises a heparin binding domain and yet the instant specification provides insufficient direction or guidance as to what sequence(s) from this region of fibronectin are sufficient to increase the number of cytotoxic cells as compared to a method performed in the absence of a fibronectin fragment.

As to practicing the claimed invention with any "precursor cell which can be formed into the cytotoxic lymphocyte," this phrase given its broadest reasonable interpretation consistent with the instant specification encompasses in its breadth, for example, using NK cells, umbilical cord blood mononuclear cells, or hematopoietic stem cells. (see instant specification paragraph bridging pages 21-22 and 38-39). While peripheral blood mononuclear cells are known to be a suitable precursor population for the differentiation of cytotoxic lymphocytes, including CTL and LAK cells (see Jung et al., 1987, J. Immunol. Vol. 139: 639-644, cited on an IDS), the use of other precursor cells for differentiation into a cytolytic lymphocyte population with fibronectin is unpredictable. For example, umbilical cord blood lymphocytes are different in phenotype and function from lymphocytes of normal adults, with cord blood lymphocytes displaying a functionally immature phenotype (see Lucivero et al., 1996, Int J. Clin. Lab Res. Vol. 26: 255-261, page 260 in particular, cited on an IDS). In fact, stimulants such as anti-CD3 fail to induce proliferation of cord blood lymphocytes (see page 260, in particular). Thus, differentiation of cord blood lymphocytes into a population of cells comprising enhanced cytolytic activity would be highly unpredictable. Additionally, hematopoietic stem cells are even more immature than umbilical cord blood cells, and attempts to obtain mature T cells by culture with IL-2 using CD34+ hematopoietic stem cells have been without notable success (see Pawelec et al., 1998, J. Leuk. Biol. Vol. 64: 733-739, cited on an IDS). Furthermore, while fibronectin enhances the cytotoxicity of cytotoxic T lymphocytes, it does not enhance natural killer cell activity (see Katzman et al., 1987, J. Lab Clin. Med. Vol. 110: 75-82 and Ybarrondo et al, Immunology, Vol. 91, No. 2, pp. 186-192, June 1997, each cited on an IDS). Thus, using fibronectin to induce longer cytotoxic activity in NK cells would be highly unpredictable.

Thus, based on the unpredictability of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. The specification demonstrates that peripheral blood mononuclear cells cultured with fibronectin can be formed into cytotoxic lymphocytes. However, no examples or guidance are provided for differentiating other precursor cells, including NK cells, hematopoietic stems cells, or umbilical cord blood cells to cytolytic lymphocytes. Therefore, based on the unpredictability of the art and the lack of guidance provided by the instant specification, it would require undue experimentation to practice the invention as broadly claimed.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-10, 12, 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frederick Darfler (WO 88/02774) in view of Ochoa et al. (Cancer Res. 1989 Feb 15;49(4):963-8), Cardarelli et al. (Cell Immunol. 1991 Jun;135(1):105-17, cited on an IDS) and Taguchi et al. (U.S. Patent 5,198,423, cited on an IDS).

Darfler teaches a method of making lymphokine activated killer cells comprising incubating PBMC on a variety of substrates, such as a polystyrene dish, with IL-2 and serum free media (see entire document, including, e.g., pages 9-13). Darfler teaches preparing LAK cells in the presence of serum-free media is advantageous because of the extreme cost of sera, its limited availability and the possibility that it might be contaminated by microorganisms, especially viruses (see page 3, 1st paragraph). Darfler further teaches that an added advantage of their method is that it permits LAK cells to be produced using less IL-2. This is important because the availability and cost of IL-2 poses a significant obstacle to the use of LAK-cell therapeutic regimens. (see page 25).

However, Darfler does not teach a method of making LAK cells in the presence of SEQ ID NO: 13.

Ochoa teaches that while LAK cells can be prepared with PBMC and IL-2 alone, addition of anti-CD3 antibodies boosts cell proliferation while maintaining LAK activity (see entire document, including the Introduction on page 963). Moreover, Cardarelli teaches the addition of immobilized fibronectin and IL-2 to PBMC cultures stimulated with anti-CD3 in the presence of serum-free media enhances proliferation and IL-2R expression of T lymphocytes (see Fig. 1 and Tables 2 and 3, in particular). Cardarelli further teaches that the regions of fibronectin responsible for its activity on T cells are the RGD cell binding domain and the EILDV amino acid sequence (see page 115, in particular). Cardarelli also teaches that the cells can be cultured at a concentration of 10^5 cells/well of a microtiter plate (i.e. at a concentration between 1 and 5 x 10^5 cells/ml).

Taguchi teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 13 (see Example 4). Said fragments comprise the RGD and EILDV sequences responsible for the activity of fibronectin on T cells as taught Cardarelli. The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

It would have been obvious to one of ordinary skill in the art to modify the method of making LAK cells taught by Darfler to include the use of immobilized anti-CD3 and fibronectin in view of the secondary reference teachings.

More particularly, one of ordinary skill in the art would have been motivated to add immobilized anti-CD3 to the Darfler method of making LAK because, as taught by Ochoa, addition of anti-CD3 antibodies boosts cell proliferation while maintaining LAK activity. One of ordinary skill in the art would have been additionally motivated to further add fibronectin to the Darfler method of making LAK because the combination of IL-2 and immobilized fibronectin + anti-CD3 is a potent stimulator of PBMC proliferation as taught by Cardarelli. One of ordinary skill in the art would further have been motivated to include immobilized fibronectin + anti-CD3 in the method of making LAK cells of Darfler because as taught by Cardarelli, the presence of immobilized fibronectin and/or anti-CD3 increases the expression of the CD25 IL-2 receptor which would reasonably suggest to one of ordinary skill in the art that these cells would have increased IL-2 sensitivity (see Cardarelli page 115, 2nd paragraph), a desirable feature as taught by Darfler. It is additionally noted that the use of serum-free media has not only the advantages taught by Darfler but also the advantage of minimizing degradation of the immobilized fibronectin as taught by Cardarelli at page 115, 1st paragraph.

As to the use of the fibronectin fragment SEQ ID NO: 13 in the method for preparing cytotoxic lymphocytes, the ordinary artisan would have been motivated to substitute the recombinant fibronectin fragment of Example 4 taught by Taguchi for the purified human fibronectin taught by Cardarelli since Taguchi teaches recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of successfully substituting the recombinant fibronectin fragment of Taguchi for purified human fibronectin because recombinant fibronectin is a biologically active fragment comprising the sequences taught by Cardarelli as being important for T cell simulation.

As to claims reciting steps of diluting or exchanging the cell culture medium, or exchanging the cell culture equipment, both Darfler and Ochoa teach numerous conditions wherein diluting or exchanging the cell culture medium is a useful step, such as in the instance of cell over-crowding, and these techniques are well known to one of ordinary skill in the art (see Darfler at page 18-19 bridging paragraph as well as Ochoa at page 963, materials and methods.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frederick Darfler (WO 88/02774) in view of Ochoa et al. (Cancer Res. 1989 Feb 15;49(4):963-8), Cardarelli et al. (Cell Immunol. 1991 Jun;135(1):105-17, cited on an IDS) and Taguchi et al.

(U.S. Patent 5,198,423, cited on an IDS) as applied to claims 1-10, 12, 13, 15 and 16 above, and further in view of Chen et al. (J Immunol. 1994 Oct 15;153(8):3630-8, cited on an IDS).

The combined teachings of Darfler, Ochoa, Cardarelli and Taguchi are described above.

They do not teach transducing a foreign gene into the T cells.

Nevertheless, Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce LAK cells with a retrovirus encoding PKC as taught by Chen. It would have been obvious to one of ordinary skill in the art that a retrovirus encoding PKC is alternative way to increase PKC activity consistent with the teachings of Darfler at page 5, 1st paragraph and pages 19-22.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-8, 10, 12, 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sagawa et al. (WO 02/14481, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (RI Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS), as evidenced by the teachings of Sagawa et al. (US 2005/0042208, cited on an IDS) which is the U.S. National Stage Application based on Sagawa WO 02/14481.

As a preliminary matter, it is noted that the teachings of Sagawa '481 are put forth in the context of the English language U.S. National Stage entry of '481, the Sagawa US 2005/0042208 publication. Nonetheless, Sagawa '481 is applied as a 102(b)/103 type reference.

Sagawa teaches a method for preparing a cytotoxic lymphocyte characterized in that the method comprises a step of induction from naive T cells which can be formed into the cytotoxic lymphocytes wherein the method includes plate bound fibronectin fragment represented by SEQ ID NO: 13 (see, e.g., pages 8-9, paragraph [0122]-[0137] and Example 12 on page 27). Sagawa also teaches the cell densities and culturing steps of the instant claims, see, ibid.

While Sagawa teaches their method is not limited to any particular medium (see paragraph [0128]) it does not explicitly teach the use of serum-free medium.

However, as taught by Darfler it was common knowledge in the art when making cells for use in adoptive immunotherapy, serum-free media is advantageous because of the extreme cost of sera, its limited availability and the possibility that it might be contaminated by microorganisms, especially viruses (see page 3, 1st paragraph).

With this common knowledge in the art in mind, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to make use of either a low serum or a serum-free media to carry out the method of Sagawa.

Such media was commonly used in the art of mammalian cell culture as taught by Freshney (see entire document). Furthermore as taught by Johnson isolated T cells grown in the presence of serum-free medium, sepahrose bound-anti-CD3 and IL-2 reach maximal proliferation levels equivalent to growth in medium + 10% FCS (see Table 1). Given the teachings of Freshney and Johnson one of ordinary skill in the art would have had a reasonable expectation of successfully practicing the method of Sagawa in no or low serum medium.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sagawa et al. (WO 02/14481, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (RI Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS), as evidenced by the teachings of Sagawa et al. (US 2005/0042208) which is the U.S. National Stage Application based on Sagawa WO 02/14481 as applied to claims 1-8, 10, 12, 13, 15 and 16 above, and further in view of Chen et al. (J Immunol. 1994 Oct 15;153(8):3630-8, cited on an IDS).

The combined teachings of Sagawa, Johnson, Darfler and Freshney are described above.

They do not teach transducing a foreign gene into the T cells.

Chen teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce the cytotoxic T lymphocytes made by the method of Sagawa, Johnson, Darfler and Freshney with a retrovirus encoding PKC as taught by Chen.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-8, 10, 12, 13, 15, 16, 20 and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 10, 12, 28, 29, 31-35 and 37-39 of copending Application No. 10/509,055 (20050227354, cited on an IDS) in view of Johnson et al. (J Immunol. 1992 Jan 1;148(1):63-71, cited on an IDS), Frederick Darfler (WO 88/02774) and Animal Cell Culture, a practical approach (RI Freshney ed., IRL Press, 1986, pp 26-41, cited on an IDS).

The reference claims are drawn to methods of preparing cytotoxic cells by culturing precursor cells capable of differentiating into cytotoxic lymphocytes in the presence of SEQ ID NO: 13.

While the reference claims do not explicitly recite growth in medium containing less than 5% serum, it would have been obvious to one of ordinary skill in the art to use such media given the teachings of Johnson, Darfler and Freshney as put forth in Section _ above.

This is a provisional obviousness-type double patenting rejection.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Primary Examiner, Art Unit 1644